## Remarks

Claims 1-5, 14-16, 18-23, 25, 27, 29, 30, 38, and 45 were previously pending in this application. Claims 14-16, 23, 25, 27, 29, 30, 38, and 45 which are now withdrawn from consideration are cancelled. Claims 1, 5, and 18 have been amended. New claims 47-50 have been added. As a result claims 1-5, 18-22, and 47-50 are pending for examination with claims 1, 18, and 47 being independent claims. Claims 1 and 5 have been amended to clarify claim language. Claim 18 has been amended to overcome an objection pertaining to a dependency from non-elected claim 14. New claims 47-50 correspond to the subject matter of claim 15, 16, 20 and 22 as filed. No new matter has been added.

## Allowable Subject Matter

Applicants acknowledge that claims 2-4 have been objected as being dependent upon an objected base claim but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims.

## Rejections Under 35 U.S.C. §112

The Examiner rejected claims 18, 20, and 22 under 35 U.S.C. §112, first paragraph as not enabled by the specification as filed. Applicants respectfully traverse the rejection.

The Examiner asserts that the specification while enabling for DNA isolated from a dog, with SEQ ID NO:1 encoding a polypeptide with SEQ ID NO:2, does not reasonably provide enablement for *any* DNA source encoding P-glycoprotein including fragments, variants, mutants and recombinants. The Examiner stated that the scope of claims 18, 20, and 22 is so broad as to encompass *any* DNA isolated from any source capable of encoding P-glycoprotein polypeptide or fragment thereof, and vectors and host cells comprising such DNAs is not commensurate with the enablement provided by the disclosure.

Applicants disagree with the Examiner for at least the following reasons. Applicants respectfully note that claim 18, as currently amended, is directed to isolated nucleic acids that encode functional P-glycoproteins comprising at least one of the specifically enumerated amino acids from dog P-glycoprotein and not *any* DNA capable of encoding P-glycoprotein polypeptide or fragment thereof. P-glycoprotein-encoding sequences are known in the art and

can be substituted with one or more of the enumerated dog amino acids to create a novel P-glycoprotein-encoding sequence. Only routine experimentation is required to test the substituted P-glycoprotein sequence (e.g. by expressing the protein and testing for P-glycoprotein activity). Therefore, it would not require undue experimentation to practice the invention claimed in claim 18.

Similarly, newly added claims 47-50 are directed to human P-glycoproteins comprising at least one amino acid of a dog P-glycoprotein at specified positions in the sequence. Claims 47-50 are not directed to, and do not encompass, *any* DNA isolated from *any* source capable of encoding P-glycoprotein polypeptide or fragment thereof, and vectors and host cells comprising such DNAs. Dog and human P-glycoproteins have been identified, sequenced, their nucleic acid sequences are available in public domains and have been provided as part of the specification (Dog P-glycoprotein SEQ ID NOs: 1, 3, 5, 24, and 26; Human P-glycoprotein SEQ ID NOs: 7 and 8).

The Examiner asserted that the Applicants propose to use the claimed polynucleotides for a variety of purposes such as recombinant protein preparation, hybridization probes and for identification of mRNA of interest. The Examiner asserts that changing the nucleotide sequences as proposed by the Applicants may not lead to desired function of the polynucleotides because the changes suggested by the Applicants will result in an enormous number of nucleotide sequences that will hybridize to several unrelated mRNAs instead of hybridizing specifically to the mRNA of interest and similarly may hybridize to cDNAs totally unrelated to cDNA of interest.

Applicants respectfully disagree. The changes suggested by the Applicants are substitutions at specific positions in known nucleic acid sequences, such as human P-glycoprotein sequences. These substitutions will, therefore, result in a limited number of nucleotide sequences and not in an *enormous* number of nucleotide sequences. Having described the amino acids that can be substituted by dog amino acids, Applicants have enabled one of ordinary skill in the art to identify and isolate nucleic acid molecules that are similar or highly homologous and that should hybridize under stringent conditions to specific sequences or their complement. Nucleic acid hybridization is well known in the art, well understood, and completely routine for one of ordinary skill in the art. Nucleic acid hybridization is ,

however, somewhat irrelevant to the enablement of the claims, as the claims recite specific sequences and/or specific substitutions of sequences to make nucleic acid molecules that encode functional P-glycoproteins.

The Examiner also asserts that it is not routine in the art to screen multiple substitutions or modifications of nucleotides as encompassed by the instant claims and that base changes within a nucleic acid's sequence can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited and the result of such modifications is unpredictable. The Examiner asserts that the specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA encoding a P-glycoprotein activity because the specification does not establish regions of the DNA sequence which may be modified without affecting the above mentioned activity/utility, the tolerance of the P-glycoprotein to modification, a predictable scheme for modifying any P-glycoprotein with an expectation of obtaining the desired biological function, and the lack of sufficient guidance as to which of the possible choices is likely to be successful.

Applicants respectfully disagree. Applicants identified the specific regions of the DNA that can be modified and provided in the Examples (Example 2) assays to assess activity and biological function of the P-glycoprotein. Applicants identified several novel dog P-glycoprotein DNA sequences (SEQ ID NO: 1, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26) and demonstrated that these sequences code for an active P-glycoprotein. Applicants claim nucleic acids that encode these dog P-glycoproteins (claims 1-5), nucleic acids that encode P-glycoproteins that have an amino acid sequence of human P-glycoprotein with one or more dog P-glycoprotein amino acid substitutions (claims 47-50), and nucleic acids that encode P-glycoproteins having one or more dog P-glycoproteins amino acid substitutions (claims 18-22, and 47-50).

The activity of the P-glycoproteins (dog, human, and other species) and their amino acid sequences are known. The nucleotide sequences that encode these amino acid sequences is known or can be deduced from the genetic code. Accordingly, one of ordinary skill in the art can determine the nucleotide sequences of the claimed nucleic acids without requiring undue experimentation, and also will have a reasonable expectation of success given that the functionality of the P-glycoproteins encoded by all input sequences is known. For example,

substitutions of dog amino acid into human P-glycoprotein sequences are very likely to produce a protein with P-glycoprotein activity, given that both the human and dog proteins are active. Thus, single and multiple substitutions can be made with an expectation that the substituted product will be active. As noted before, nucleotide sequences for any of these substituted proteins can be deduced readily using a software package that translates sequences, or even by hand. The activity of substituted P-glycoproteins can be readily tested using standard assays some of which are described in the application

Moreover, Applicants maintain that full consideration of each and all of the *Wands* factors, in view of the state of the art at the time of filing, leads one to the reasonable conclusion that practicing the invention would not require undue experimentation. *In re Wands* 858 F.2d 731, 737, 740, 8 USPQ2d 1400, 1404, 1407 (Fed. Cir. 1988). Applicants do not agree with the Examiner's assertion that no guidance was provided. As noted above, Applicants' specification provided ample guidance to one of ordinary skill in the art at the time of filing how to make, test and use the claimed nucleic acids.

Considering the remaining *Wands* factors, the quantity of experimentation to obtain the claimed nucleic acid molecules is not undue given that Applicants have provided one of ordinary skill in the art with the sequence of the entire DNA molecule and P-glycoprotein sequences from species other than dog are known in the art. Applicants have provided guidance in both working examples and other portions of the specification.

Neither the scope of the claims nor the nature of the invention is overly broad, again because there is a limitation on the sequence of the claimed nucleic acid molecules.

Moreover, as in the *Wands* case, because of the "high level of skill in the art at the time the application was filed" and because "all of the methods needed to practice the invention were known," the claimed invention is enabled by the specification. *Wands* at 740, 8 USPQ2d at 1406. Applicants maintain that the same conclusions with respect to the state of the art and the level of skill in the art are true in the instant case, and, therefore, must weigh heavily in favor of a finding that routine experimentation and not undue experimentation is required to practice the invention commensurate with the scope of the claims.

The Examiner rejected claims 18, 20, and 22 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Applicants, at the time of the application was filed, had possession of the claimed invention. The Examiner asserts that the claims are directed to a genus of DNA molecules encoding P-glycoprotein or a fragment thereof and that the specification does not contain any disclosure of the structure of all DNA sequences that encode any glycoprotein or fragment thereof. According to the Examiner, the genus of DNAs claimed in the instant invention is a large variable genus with the potentiality of having many different structures, and, therefore, many structurally unrelated DNAs are encompassed within the scope of these claims. The Examiner asserts that specification discloses only a single species (SEQ ID NO:1) of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all the species within the claimed genus and that one skilled in the art cannot reasonably conclude that the Applicants had possession of the claimed invention at the time the instant application was filed.

Applicants respectfully traverse the rejection for the following reasons. Applicants have provided the amino acid sequence of dog P-glycoprotein. Other P-glycoprotein amino acid sequences, including human, are known. The nucleotide sequences encoding these polypeptides also are known, or can be provided simply by applying the genetic code to "reverse translate" an amino acid sequence into a set of nucleotide sequences. A person skilled in the art could recognize, therefore, that Applicants were in possession of the claimed invention, because Applicants provided the sequences and specific positions at which substitutions are to be made within an amino acid sequence. Therefore, Applicants have disclosed many more species than just one as alleged by Examiner. The written description of the invention in the specification as filed teaches one of ordinary skill in the art how to make and use the claimed invention throughout its scope (see below). Given that the invention was enabled by the specification as filed, the invention was also fully described at the time of filing in full, clear, concise and exact terms.

The court in the *Lilly* case stated that a proper written description "of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of

structural features common to the members of the genus, which features constitute a substantial portion of the genus. This is analogous to enablement of a genus under §112, paragraph 1, by showing the enablement of a representative number of species within the genus." *Regents of the University of California v. Eli Lilly and Co.* 43 USPQ 2d 1398 (Fed. Cir. 1997). In the instant application, Applicants recited a representative number of DNAs, defined by nucleotide sequences that fall within the scope of the genus, i.e., by recitation of amino acid sequences of P-glycoproteins (dog P-glycoprotein, human P-glycoprotein, etc.) which is an inherent disclosure of nucleotide sequences that encode the amino acid sequences. Thus Applicants were in possession of the claimed invention at the time of filing and the invention was placed into the possession of one of ordinary skill in the art by the written description contained in the specification as filed.

The claims at issue are specifically directed to "isolated nucleic acid molecules" that have the specific sequences and sequences with substitutions at specific locations recited in the specification. One of ordinary skill in the art would know that Applicants, having provided specific nucleotide sequences and amino acid sequences of dog P-glycoprotein and substituted P-glycoproteins, were in possession of the invention as of the time of filing of the application.

The Examiner stated that "the specification discloses only a single species (SEQ ID NO:1) of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all the species within the claimed genus." Applicants respectfully contend that this is incorrect because the specification describes a large number of nucleotide sequences by virtue of providing amino acid sequences that explicitly define the claimed genus of nucleotide sequences. Thus, the specification provides the nucleic acid sequences and degenerate nucleotide sequences (from the amino acid sequences) readily visualized by one of ordinary skill in the art. The specification conveys to one of ordinary skill in the art that Applicants were in possession of the claimed invention. Thus the specification meets the standard set forth in the case law for written description of a nucleic acids.

The Examiner stated that the genus is a large variable genus with the potential of having many different structures and that the specification discloses only a single species of the claimed genus one of ordinary skill in the art would "reasonably conclude" that the specification does not provide a representative number of species to describe the genus.

Applicants have described a number of species in the specification that the Examiner apparently has not considered.

The Examiner must keep in mind that the specification is written for one of ordinary skill in the art. Therefore, the proper inquiry is whether the specification has described a number of species through the various descriptions of nucleic acid species in the specification so that Applicants' possession of the claimed invention was reasonably conveyed to the person of skill in the art. Applicants contend that one of ordinary skill in the art would readily recognize that Applicants had possession of the invention based on the various described species of nucleic acids and amino acid sequences, just as if the specification set forth a large number of these molecules by mechanical substitution of individual nucleotides in the described nucleic acid molecules.

Accordingly, Applicants respectfully request that the Examiner withdraw the claim rejections under 35 U.S.C. §112 first paragraph as containing subject matter which is not described in the specification in such a way as to convey to one skilled in the relevant art that the Applicants, at the time of the invention, had possession of the invention.

Claims 1, 5, and 18-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification. Claims 1, 5, and 18 are directed to allelic variants of polynucleotides but there is no specific definition in the specification for allelic variant.

Claims 1 and 5 have been amended. The amendments to claims 1 and 5 obviate the rejection.

In view of the foregoing arguments, Applicants respectfully request that the Examiner withdraw the rejections made under 35 U.S.C. §112, first paragraph.

**Rejections Under 35 U.S.C. §102**

The Examiner rejected claims 1, 5, and 18-22 under 35 U.S.C. §102(b) as being anticipated by Steingold et al.

Although Applicants disagree with the Examiner's conclusions regarding Steingold et al, claims 1 and 5 have been amended to remove "allelic variants" from the claims. Accordingly, withdrawal of this rejection is respectfully requested.

**Conclusion**

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of the claims. If the Examiner wishes to advance the prosecution, or if the amendment is defective or unclear, then the Examiner is invited to telephone the undersigned at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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Docket No. G00307.70017.US
Date: June 12, 2003
**x06/12/03**